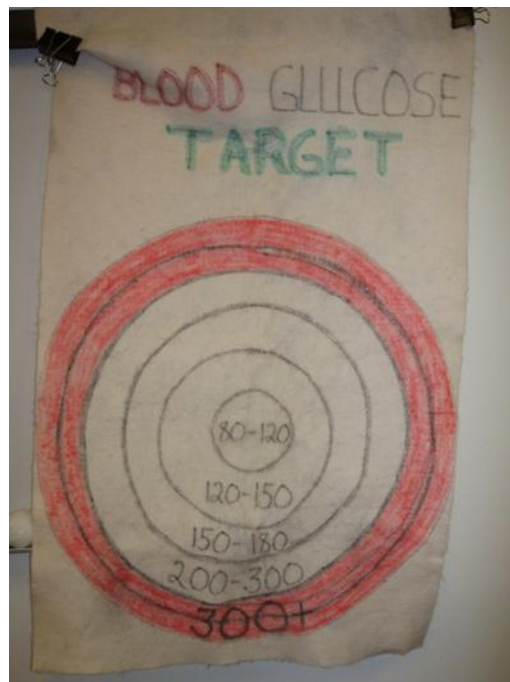


The implementation of guidelines in clinical practice

- *Benefits and challenges exemplified by international guidelines in Diabetes Mellitus in children*



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Abstract

Background:

Diabetes mellitus is a group of chronic metabolic diseases characterized by high concentration of glucose in the blood. The most common form of diabetes among children and adolescents is type 1 diabetes (T1D). This is the second most common chronic disease acquired in childhood and adolescence, and the incidence is increasing globally. The disease is associated with autoimmunity and complications causing high morbidity and mortality. With the globalization, the need of international consensus is increasing in medicine. International and national guidelines are established for diagnostics, treatment and follow up of children with diabetes to optimize treatment and reduce complications. Guidelines are mainly worked out with reference to medicine in the western world.

Aims:

The aim of this study is to explore and discuss the challenges in implementing internationally agreed guidelines in clinical practice in two hospitals in USA and one in Norway. To assess this, we used established guidelines for diabetes; International Society of Pediatric and Adolescence Diabetes (ISPAD) and American Diabetes Association (ADA). Many aspects of these guidelines are transferable to other medical conditions as T1D is a chronic disease, acquired early in life, demanding lifelong treatment and with a potential risk of complications. Our thesis is part of a larger project where the aim is a comparison of strategies towards implementing internationally agreed guidelines in different countries. Our group of 12 students has been in different parts of the world.

Methods:

We made an electronic questionnaire based on the 2009 ISPAD's and ADA's guidelines. The questionnaire was designed to collect information about T1D in children less than 15 years of age. Health personnel were interviewed and the survey contains no personal identifiable data. We did our interviews at Children's Hospital of Orange County (CHOC) in California, University of Minnesota Amplatz Children's hospital in Minneapolis and Ullevål University Hospital in Oslo.

Results:

Our results mainly refer to children younger than 18 years of age. Exclusive data from children less than 15 years were not available. All the hospitals we visited used guidelines in their clinics. At CHOC they used ADA's guidelines, in Minneapolis and Oslo ISPAD's guidelines were adhered to. There are discrepancies between the treatment goals in ISPAD's and ADA's guidelines. At CHOC the insulin treatment was not optimal according to the ADA recommendations of multi-injection therapy for all age groups, with a two-shot regimen for all children in school age, mainly due to practical and economic reasons.

Discussion:

Challenges in implementing guidelines are mainly economical and practical, also in the western part of the world. The challenges are probably even greater in countries where there is lack of high quality health facilities and resources, and a less well organized health care system for all.

Conclusion:

Guidelines are important tools in the diagnostics, treatment and follow up of patients with chronic diseases. They help to manage the disease in a standardized and consistent way according to the best international knowledge. However, local adjustments have to be made.

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We made the questionnaire during the spring 2009, together with our student colleagues Martine A. Munkvold, Lene Sleire, Natalie L. Berntsen and Eirin Eilertsen. Diabetes nurse Siv Janne Kummernes was helpful with the first testing of the questionnaire. We would also like to thank Haneef Awan who made the electronic version of the questionnaire.

We visited Children's Hospital of Orange County (CHOC) in California, the University of Minnesota Amplatz Children's hospital in Minneapolis and Ullevål University Hospital in Oslo. We are grateful to the diabetes teams who welcomed us and let us observe their work. Especially we want to thank Dr. Mark Daniels at CHOC for taking care of us. Ragnar Amlie organized so we could be observers at CHOC. Dr. Toni Moran in Minneapolis organized our schedule while we visited their clinic. The diabetes educators Shannon Beasley and Anne E Jackson were helpful answering all our questions. We would also like to thank the staff at ADA Diabetes Camp in Hudson, Wisconsin.

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Lise Haldorsen Willumsen and Idun Stenhammer Aanerød

Abbreviations

AC	Albumin concentration
ACR	Albumin/creatinine ratio
ADA	American Diabetes Association
AER	Albumin excretion rate
AGE	Advanced glycosylation end products
BG	Blood glucose
BMI	Body mass index
CAD	Coronary artery disease
CHOC	Children's Hospital of Orange County
CNS	Central nervous system
CSGM	Continuous subcutaneous glucose monitor
CVD	Cardiovascular disease
DCCT	The diabetes control and complications trial
DKA	Diabetic ketoacidosis
DM	Diabetes Mellitus
DPN	Distal symmetric polyneuropathy
EMA	Endomysial autoantibody
ER	Emergency room
ESRD	End stage renal disease
GFR	Glomerular filtration rate
GP	General practitioner
Hb	Hemoglobin
HbA _{1c}	Hemoglobin A 1 c
ISPAD	International Society of Pediatric and Adolescence Diabetes
JDRF	Juvenile Diabetes Research Foundation
LDL	Low density lipoprotein
NDA	Norwegian Diabetes Association
OUS	Oslo University Hospital (Sykehus)
PADRE	Pediatric Adolescent Diabetes Research Education
SMBG	Self-monitoring of blood glucose
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TDEI	Total daily energy intake
TSH	Thyroid stimulating hormone
tTG	Tissue transglutaminase
U of M	University of Minnesota
UUH	Ullevål University Hospital

Part 1: Literature review

In our literature review we searched for updated knowledge in PubMed, textbooks and the Guidelines of International Society for Pediatric and Adolescence Diabetes (ISPAD) and American Diabetes Association (ADA).

1. Introduction – Diabetes mellitus

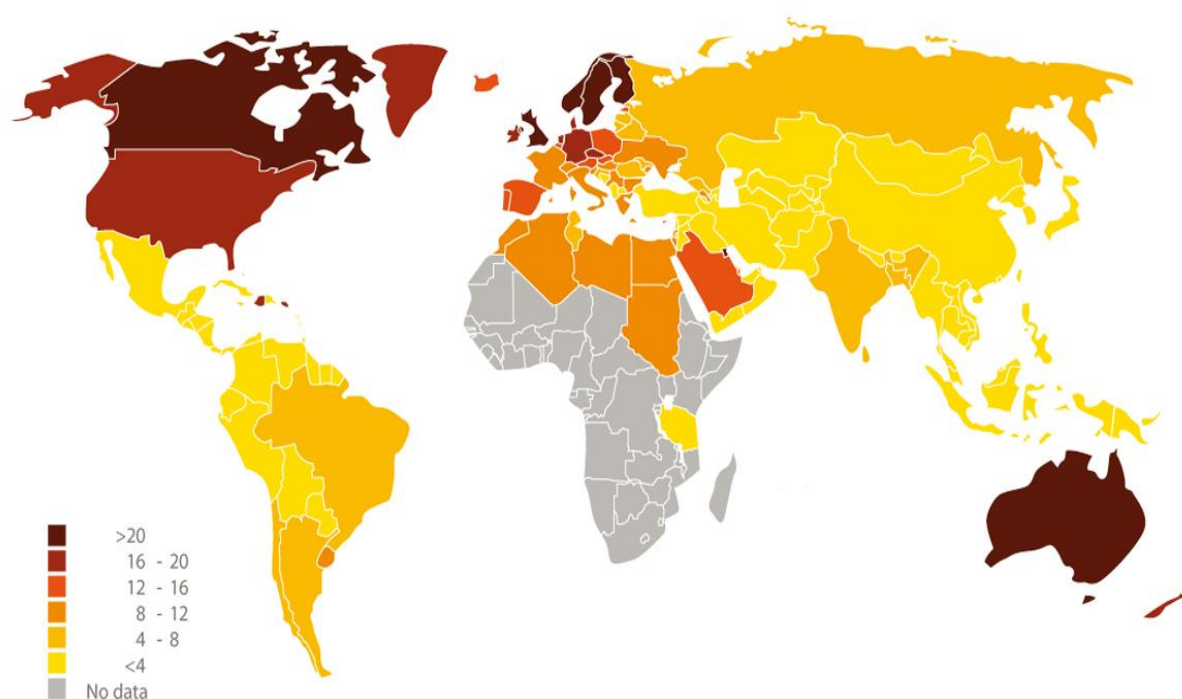
Diabetes mellitus (DM) is a group of chronic metabolic diseases characterized by high concentration of glucose in the blood. The hyperglycemia is caused by defects in insulin secretion, insulin action or both. Deficiency in insulin affects the hormone's target tissues and abnormalities in the metabolism of carbohydrates, fat and protein occur (1). Type 1 diabetes (T1D) is the second most common chronic disease in childhood and adolescence after asthma and is associated with autoimmunity and complications. Globally the incidence is increasing. The affected patients are in need of lifelong insulin replacement therapy. There are international guidelines concerning the diagnostics, treatment and follow up of pediatric diabetes. In this paper we focus on T1D which is the most common form of diabetes in childhood and adolescence, characterized by β -cell destruction, autoimmunity and insulin deficiency.

2. Epidemiology

T1D accounts for more than 90% of childhood and adolescent diabetes in most western countries. In epidemiological incidence studies, the onset of T1D is defined by the date of the first insulin injection. The incidence varies greatly between different countries, from 0.1 per 100,000 in China to 57.6 per 100,000 in Finland (Figure 1). The incidence also varies within countries and between ethnic populations. Gender differences in incidence are found in some (high incidence) populations. There is a documented rise in incidence of T1D in the world, especially in the age group less than 5 years (2). Norway is amongst the countries with highest incidence of T1D in the world (Figure 1). In 2008, 321 persons under 19 years of age were diagnosed with T1D.

Figure 1: The global incidence rate of T1D in children age 0-14 years in 2006.

Incidence rates of type 1 diabetes in children, 0-14 years (cases per 100,000 population per year)



SOURCE: DIABETES ATLAS THIRD EDITION, © INTERNATIONAL DIABETES FEDERATION, 2006

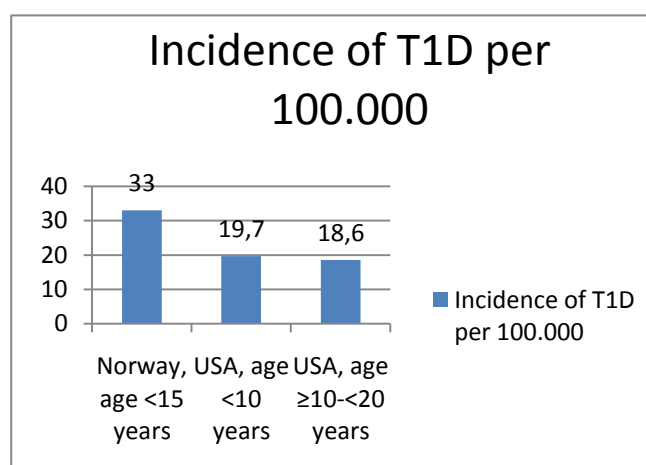
Table 1: The distribution in age groups of diagnosed T1D in Norway in 2008. Numbers from the Norwegian Childhood Diabetes Registry.

Age	Number (%)
< 15 years	303 (94)
< 10 years	154 (48)
< 5 years	60 (19)

Due to more heterogeneous ethnicity, the incidence rate of T1D varies more within USA than in Norway, where the population has been more ethnical homogenous. In the period 2002–2005, 15,600 youth were diagnosed with T1D annually in the U.S (3). Non-Hispanic white had the highest incidence; 24.8 per 100,000 per year amongst those younger than 10 years and 22.6 per 100,000 per year amongst those aged 10–19 years. This is, however, still lower than in Norway (Figure 2).

In some ethnic groups in USA, the rate of newly diagnosed T1D and type 2 diabetes (T2D) in the age group 10-19 were similar (non-Hispanic Black and Hispanic youth), in other the rate of T2D was greater than T1D (Asian/Pacific Islander and American Indian). In Norway more than 99 % of newly diagnosed pediatric diabetes is T1D. Close to 2500 children younger than 15

Figure 2: Incidence of new onset T1D. The numbers from Norway are from the National Diabetes Childhood Registry, 2008 Annual Report. The numbers from USA are from ADA's 2011 National Diabetes Fact Sheet, and represent the average annual incidence in the period 2002-2005.



years have T1D in Norway (0,27% of the population in the age group) (4;5), compared to approximately 215,000 people younger than 20 years (T1D or T2D) in the U.S. (0.26% of the population in the age group) (6).

3. Etiology

T1D is a chronic immune-mediated disease, caused by autoimmune destruction of the insulin-producing β -cells in the pancreatic islets. Genetic susceptibility, autoimmunity and an environmental insult are mechanisms responsible for the cell destruction.

Genetic susceptibility is most important linked to specific alleles in the human leukocyte antigen (HLA) class II locus, located on the short arm of chromosome 6 (7). Other genetic loci are involved but to a lesser extent. Within the HLA class II locus, genes are both protective and predisposing for T1D.

Less than 10% of genetic susceptible individuals progress to clinical disease. Thus, additional environmental factors are needed to trigger the development of the disease (8;9). Candidates are virus and dietary factors. Several ongoing studies investigate the association between these and the development of disease (The Environmental Determinants of Diabetes in the Young (TEDDY) Study, Diabetes Autoimmunity Study in the Young (DAISY) Study and Diabetes Prediction and Prevention (DIPP) Study).

A chronic autoimmune response against the pancreatic β -cells causes a selective loss of these insulin-producing cells. Markers of this immune destruction of the β -cells include islet cell autoantibodies and autoantibodies to insulin, glutamic acid decarboxylase and several other cytoplasmic proteins. At least one of these antibodies is present in 85-95% of individuals with new-onset T1D (8;10). 10-20% of the T1D patients have an additional autoimmune disorder such as Grave's disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, pernicious anemia, and celiac disease (8).

4. Diagnosis of T1D

The classical symptoms of T1D are excessive thirst, polyuria, weight loss and fatigue. When a child gets sick from diabetes the first time it is most often easy to diagnose. If this is not the case, the same criteria for diagnosis are used in children as in adults.

Table 2: Diagnostic criteria for diabetes (2;11).

1. Symptoms of diabetes plus casual plasma glucose concentration ≥ 11.1 mmol/L (200 mg/dL)*. Casual is defined as any time of day without regard to time since last meal.
OR
2. Fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL). Fasting is defined as no caloric intake for at least 8 hours.
OR
3. 2-hour post load glucose ≥ 11.1 mmol/L (≥ 200 mg/dL) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g.

*Corresponding values (mmol/L) are ≥ 10.0 for venous whole blood and ≥ 11.1 for capillary whole blood

5. Treatment of T1D

5.1 Medication

The medicines used in treatment of T1D are insulin and glucagon. Patients with T1D have lost their ability to produce insulin and are dependent on injections of insulin for survival. Insulin treatment prevents metabolic decompensation and ketoacidosis. The aim is physiological insulin replacement combined with optimal glycemic control, currently not possible to reach to the full extent. Therefore, the goal is to administer insulin to reduce the risk of long-term and acute complications.

5.1a Glucagon

Glucagon is a hormone produced in endocrine pancreas. It increases the blood glucose (BG) by releasing glycogen from the liver via stimulation of the hepatic glycogenolysis, gluconeogenesis and ketogenesis (12). Glucagon is used for injection if a person with diabetes is unconscious or unable to eat because of hypoglycemia. It is administered as a subcutaneous or intramuscular injection, but will not have effect if given after fasting or exercise when the glycogen storage in the liver is low (13).

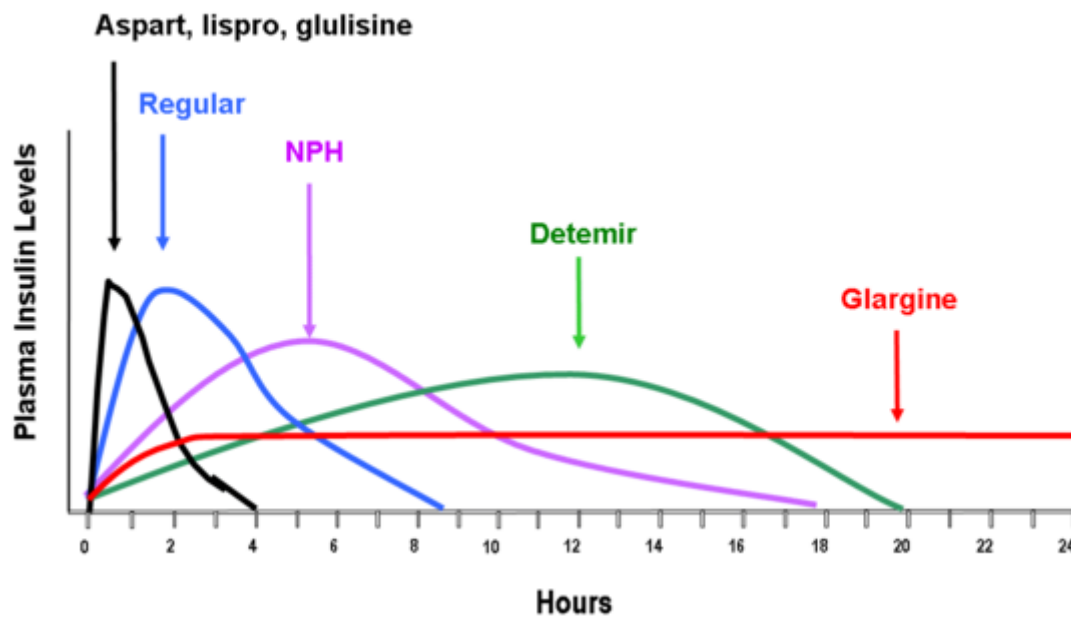
5.1b Insulin

There are different types of insulin (Table 3 and Figure 3), different ways of administration, and different regimes.

Table 3: Types (names) of insulin (13).

Type of insulin	Product
Rapid-acting	Lispro (Humalog), Aspart (Novolog), Glulisine (Apidra)
Short-acting	Regular (R), Human
Intermediate-acting	NPH (Insulatard)
Long-acting	Glargine (Lantus), Detemir (Levemir)

Figure 3: Idealized insulin time-action profiles after subcutaneous injection of the insulins; Aspart, Lispro, Glulisine, Regular, NPH, Detemir, Glargine (14).



Many factors will influence on the choice of insulin regimen; age, duration of diabetes, lifestyle, targets of metabolic control and individual patient/family preferences. More than three injections daily are called multi-injection therapy or intensive treatment. Common insulin regimens are (15);

- Two injections daily: Mixture of short/rapid acting and intermediate acting insulin.
- Three injections daily: Mixture of short/rapid and intermediate acting insulin twice daily and a third injection of short/rapid acting insulin alone.
- Basal bolus regimen: 40- 60% of the total insulin dose should be basal insulin, the rest pre-prandial rapid acting or regular insulin with meals and snacks. Intermediate acting insulin or basal/long acting analogs are administered once or twice daily.
- Insulin pump: Short acting insulin in a combination of continuous injection and bolus injections. This regimen has the best possibility of imitating the physiological insulin profile.

5.2 Monitoring of glycemic control

5.2a Self-monitoring of blood glucose (SMBG)

Daily monitoring of capillary BG level is an essential tool for optimal management of diabetes. It assists safe management of both hypo- and hyperglycemia. Hypoglycemia is a common acute complication. Predictors are age (infancy and adolescence), increased duration of diabetes, lower

glycated hemoglobin (HbA_{1c}) and higher insulin dose. Young children and their parents are more vulnerable to oversee hypoglycemic signs. Anxiety for hypoglycemic episodes may limit close BG control and be a challenging factor in the care. Early detection of low BG prior to symptoms may prevent overcorrection of hypoglycemia, causing hyperglycemia. SMBG should be done frequently to optimize each child's diabetes control as the frequency of SMBG correlates with glycemic control (16).

5.2b Urine glucose

In many countries SMBG is not available. The alternative is urine glucose. Urinary glucose reflects the glycemic levels over the preceding several hours. It is affected by the renal threshold for glucose.

5.2c Continuous glucose monitoring

Continuous glucose monitoring devices measure interstitial fluid glucose every 1-20 minutes.

Currently these devices are expensive, and they may not be available in all countries. It is anticipated that decreased BG targets can be achieved more safely as continuous glucose monitoring becomes widely available, allowing further decrease in target HbA_{1c} levels (17;18).

5.2d Glycated hemoglobin, HbA_{1c}.

The hemoglobin (Hb) molecule in the red blood cells transports oxygen throughout the body. Newly formed red cells have little glucose attached. Erythrocytes are freely permeable to glucose. The result is glucose irreversibly bound to Hb. The rate of this process is dependent upon the prevailing glucose concentration. Average lifespan of an erythrocyte is 120 days, with approximately 1% destroyed and replaced every day. Thus, the average amount of HbA_{1c} changes in a dynamic way and indicates the mean blood glucose concentration over the life span of the erythrocyte. HbA_{1c} is the only measure of glycemic control for which robust outcome data are available. Elevated HbA_{1c} predicts long-term micro- and macrovascular complications. Improved glycemic control is associated with less, and delayed microvascular complications (19;20). Both hypoglycemia and hyperglycemia may result in central nervous system (CNS) alterations, both acutely and chronically (21;22).

Figure 4: Comparison of quarterly mean blood glucose concentrations with quarterly HbA_{1c} values. The green lines represent 95 percent confidence intervals for individual values. The observed relationship applies only to the Diabetes Control and Complications Trial assay or to assays which have been standardized to it (23). To convert blood glucose values to mmol/L, multiply by 0.056.

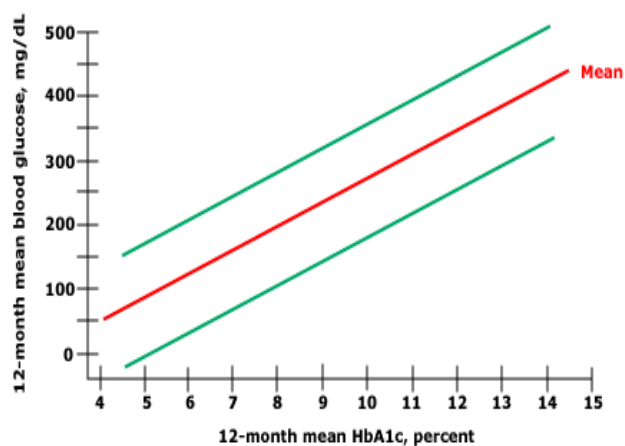
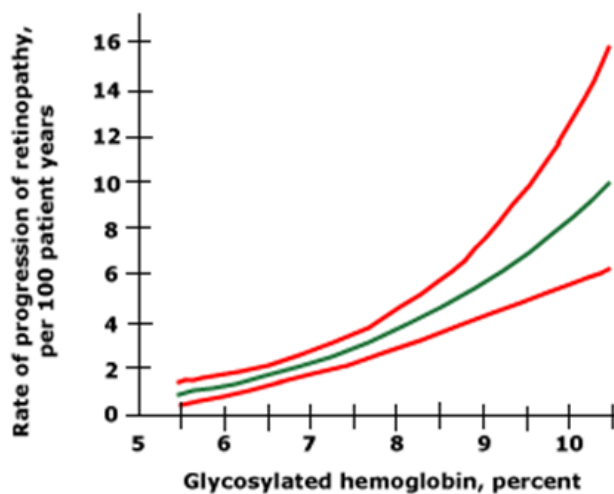


Figure 5: Risk of sustained progression of retinopathy in patients with type 1 diabetes according to the mean glycosylated hemoglobin values at six-month intervals (green line). Better glycemic control was associated with a lesser rate of progressive retinopathy. The red lines represent the 95 percent confidence intervals (20).



5.2e Urinary or blood ketones

Ketones are monitored during uncontrolled hyperglycemia, insulin deficiency and days of clinical sickness.

5.3 Education

Education is a keystone of diabetes care. Systematic reviews of psycho-educational interventions show small to medium beneficial effects on glycemic control and somewhat greater effects on psychological outcomes in

Figure 6: Dr. Elliot Joslin



*"Diabetes education
is not an element in
the treatment...
...it is the treatment"*

Dr. Elliot Joslin (USA) 1920

children and adolescents (24;25). The best effects are achieved when parents are involved in the treatment and education. Important areas of focus are problem-solving, goal setting and self-efficacy. Effective self-management requires frequent and high levels of educational input and support. Children, adolescents and their caregivers should be included in the easy access educational process. Education should be provided by trained healthcare professionals in a continuous process to be effective. Additionally, it should be personalized to suit each individual's needs. At diagnosis the basic needs for survival has to be taught. This includes simple explanations of the diagnostic process, what has caused the symptoms and the consequences of the disease. One needs to talk about glucose and insulin, and how this works in the body. Furthermore, the influence different factors in everyday life, like illness, exercise and food intake have on the BG must be discussed. The patient and caregivers must also learn practical skills of how to make insulin injections, measure BG and test the urine for ketones. Acute complications must be explained; the symptoms and how to treat it (26).

5.4 Screening for complications and associated diseases

Late complications are the major cause of morbidity and mortality in T1D. Screening for these complications aims at detecting them when they are subclinical and treat them to delay progression to clinical disease. The screening tests relate to potential affected organs; the kidney, the eye, the nervous

system and vasculature (27). Early detection of possible associated autoimmune diseases is important to improve quality of life. Screening include test for celiac disease and thyroid function (28;29).

5.5 Nutrition

Nutritional management is another cornerstone of diabetes care. A specialist pediatric dietitian with experience in diabetes care should be available to provide nutritional education. The first contact with a dietitian should happen as soon as possible after diagnosis to develop a lasting and trusting relationship.

Growth monitoring is essential. The energy intake and essential nutrients should aim to maintain an ideal body weight and secure optimal growth, health and development and prevent acute and chronic complications. Total daily energy intake (TDEI) should be distributed to less than 50 % carbohydrate, less than 35% fat and 10-15% protein. Quantification of carbohydrate intake with appropriate insulin adjustments requires a higher level of structured education, monitoring and support to be successful. However, there is no strong research evidence to demonstrate that one particular educational tool or method of quantifying carbohydrate intake is superior to another (30).

Nutritional advice must be adapted to cultural, ethnic and family traditions and the psychosocial needs of the individual child. Regularity in meal times and eating routines are important. The choice of insulin regimen should take into account the dietary habits and lifestyle. Conventional insulin regimens demand some consistency in carbohydrate intake to be successful. Intensive insulin regimens allow greater flexibility as long as the matching of insulin doses to carbohydrate intake is understood and applied (30).

5.6 Islet cell transplantation

Currently islet of Langerhans transplantation is used only in a select group of patients with T1D with severe glycemic lability, recurrent hypoglycemia and hypoglycemia unawareness. The procedure is minimal invasive, with few procedure-related complications. The islets are infused percutaneously via a catheter into the hepatic portal vein. Most patients need insulin by five years post-transplantation owing to decline in graft function, but the beneficial effects on the frequency of hypoglycemic

episodes and hypoglycemia awareness remain. Most long term complications are related to systemic immune-suppression (31).

6. Pathology and complications in T1D

The complications lead to increased morbidity and mortality and are divided into acute and long term.

The long term complications are divided into micro and macrovascular ones.

6.1 Acute complications

Acute complications in T1D are diabetic ketoacidosis (DKA) and hypoglycemia which are the major causes for death in T1D less than 30 years of age (32;33).

6.1a Diabetic ketoacidosis

DKA results from absolute or relative insulin deficiency coupled with the effects of the counter regulatory hormones like catecholamines, glucagon, cortisol and growth hormone. Absolute insulin deficiency occurs in undiagnosed T1D and in patients on treatment when the delivery of insulin fails. Relative insulin deficiency occurs when the counter regulatory hormones increase in stress conditions like sepsis, trauma or gastrointestinal illness with diarrhea and vomiting (34).

The hormone shifts in T1D causes a catabolic state which affects the metabolism of glucose, fat and protein. In lack of insulin, glucose production is increased in the liver through glycogenolysis and gluconeogenesis, and utilization of glucose is decreased in muscle and adipose tissue. The combined result is hyperglycemia and hyperosmolality. Insulin deficiency also induces increased lipolysis and ketogenesis, causing ketonemia and metabolic acidosis. Increased protein catabolism aggravates the ketogenic state. DKA is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid compartments. BG levels that exceed the renal threshold (approximately 10 mmol/L [180 mg/dL]) and hyperketonemia cause osmotic diuresis leading to dehydration and loss of electrolytes. The clinical manifestations and signs of DKA include: dehydration, nausea, vomiting, abdominal pain mimicking an acute abdomen, rapid and deep sighing (Kussmaul respiration), progressive obtundation and loss of consciousness, increased leukocyte count with left shift, non-specific elevation of serum amylase and fever if infection is present.

6.1b Hypoglycemia

Hypoglycemia is a potential complication to the treatment of T1D. It results from a mismatch between circulating insulin, food intake and recent physical activity and is rarely a spontaneous event. The brain is dependent upon glucose for metabolism. Hypoglycemia is feared because of its correlation with permanent neurological sequelae and death (21). There is no consistent numerical definition of hypoglycemia in children but an agreement that BG values below 3.3-3.9 mmol/L (60-70 mg/dL) places the individual at risk for developing severe hypoglycemia. According to ISPAD and ADA, the recommended lower target for BG is 3.9 mmol/L (70 mg/dL). The severity of hypoglycemia is divided into mild/moderate and severe. In severe hypoglycemia the child has altered mental status, is unable to assist in its own care and may/may not have convulsions. Repeated episodes of mild/moderate hypoglycemia may have impact on the child's daily life, school and social performance. Repeated episodes of hypoglycemic seizures may cause permanent changes to the brain and affect language and memory (35).

If the blood sugar falls, symptoms of hypoglycemia might occur; autonomic (adrenergic) activation and/or neurological dysfunction (neuroglycopenia). The BG threshold for autonomic activation is related to activation of counter regulatory hormones. The threshold for this varies with age and the level of BG control. When this occur the BG level may vary amongst individuals and from episode to episode for the same individual. After a hypoglycemic event the awareness of symptoms may be reduced for 24 hours. Neuroglycopenia is not affected by BG control and previous hypoglycemic episodes. If it occurs before autonomic activation, the awareness of hypoglycemia is reduced. This phenomenon is named hypoglycemia unawareness and is the cause in many hypoglycemic events. Hypoglycemia unawareness may be reversed by 2-3 weeks avoiding hypoglycemia.

6.2 Long term complications

The time of onset and severity of late complications varies greatly among the T1D patients. Patients with rigid diabetes control may have delayed onset. Experimental studies and clinical evidence suggests that most complications of diabetes result from metabolic derangements, mainly

hyperglycemia. Two mechanisms are considered important; non-enzymatic glycosylation and intracellular hyperglycemia.

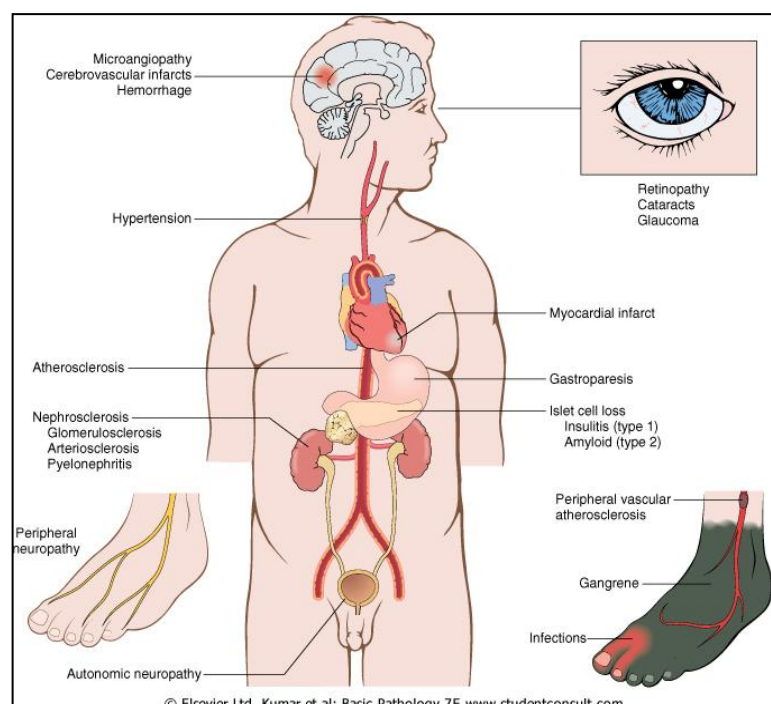
Non-enzymatic glycosylation: In this process glucose attaches to free amino groups without the aid of enzymes. The degree of glycosylation directly correlates to the level of blood glucose. In interstitial tissues and blood vessel walls proteins finally accumulates as advanced glycosylation end products (AGE's). These products can trap other plasma and interstitial proteins, like low density lipoprotein (LDL) in the intima of the vessel wall, causing deposition of cholesterol. AGEs may also cause microangiopathy, which is affection of the function and structure of capillaries including renal glomeruli, resulting in thickened basement membranes and more leaky capillaries (8).

Intracellular hyperglycemia: Nerves, lens, kidney and blood vessels do not require insulin for glucose transport. Hyperglycemia will lead to an increase in intracellular glucose. Inside the cell the glucose is metabolized to sorbitol, and eventually to fructose. Accumulation of these substances leads to increased intracellular osmolarity and influx of water, resulting in osmotic cell injury. Sorbitol accumulation also impairs ion pumps and is believed to promote injury of Schwann cells and pericytes of retinal capillaries. Peripheral neuropathy and retinal microaneurysms may be the result (8).

6.2a Microvascular complications

These complications include retinopathy, nephropathy, and neuropathy. The clinical outcomes are visual impairment and blindness in diabetic retinopathy, renal failure and hypertension in diabetic nephropathy and pain, paraesthesiae, muscle weakness and autonomic dysfunction in diabetic neuropathy (27).

Figure 7: Organs potentially affected by diabetes.



The diabetic retinopathy is a well-characterized constellation of changes that to some degree develops in nearly all patients with diabetes. It is the leading cause of blindness among people of working age in the Western world (36). Adolescents have a higher risk of progression to vision threatening retinopathy compared to adult patients with diabetes (27).

The retinal lesion has two forms: background or non-proliferative retinopathy and proliferative retinopathy. In both forms the alterations are in the microvasculature with areas of non-perfusion and increased vasopermeability. The proliferative form additionally has neovascularization.

The background or non-proliferative retinopathy is characterized by microaneurysms, hemorrhages, microinfarction (soft exudates) and protein and lipid leakages (hard exudates). Intra-retinal microvascular abnormalities with dilatation, constriction and tortuous vessels are also seen. Background retinopathy is not vision-threatening and does not invariably progress to proliferative retinopathy (27).

The proliferative retinopathy is characterized by neovascularization in the retina and/or the vitreous posterior surface. The retinal vessels may rupture or bleed into the vitreoretinal space. This is vision-threatening. Fibroblast activation may lead to adhesions, which again increases the risk of hemorrhage and retinal detachment. High-risk characteristics for visual loss are location and extent of neovascularization and vitreous or pre-retinal hemorrhage (27).

Maculopathy is characterized by decreased vascular competence and micro aneurysms with exudation and swelling in the central retina (27).

Nephropathy progresses clinically from normoalbuminuria, through a subclinical stage of increased urinary albumin excretion (microalbuminuria) and overt proteinuria, eventually to end-stage renal disease (ESRD). ESRD usually occur after many years and requires dialysis or kidney transplantation. At the earlier stages, the renal disease may stop, regress or progress.

Microalbuminuria (27) is confirmed by consistent findings, meaning abnormal findings in 2 or all of 3 samples over a 3–6 month period. Persistent microalbuminuria has been shown to predict the progression to ESRD and is associated with an increased risk of macrovascular disease. An increase of albumin excretion rate (AER) within the microalbuminuric range identifies patients at risk of progression to renal damage. Screening from age 11 years with 2 years diabetes duration and from 9

years with 5 years duration will capture most evolving microalbuminuria in children and adolescents (27).

Diabetic nephropathy is defined as persistent proteinuria greater than 500 mg/24 hours or albuminuria greater than 300 mg/24 hours. Usually, diabetic nephropathy is associated with hypertension, and a diminishing glomerular filtration rate (GFR) (27). Diabetic nephropathy is a major cause of morbidity and mortality amongst young adults with T1D. Early detection of diabetic nephropathy and timely treatment of blood pressure have a pivotal role in the prevention of ESRD in young people and adults with diabetes (27).

Diabetes additionally can affect the somatic and autonomic nervous system, central as well as peripheral. The somatic neuropathies associated with diabetes are the focal and the generalized neuropathy. Focal neuropathies include mononeuropathies such as carpal tunnel syndrome, palsy of the peroneal nerve causing sudden foot drop or isolated cranial nerve palsies.

Diabetic sensorimotor polyneuropathy is the most common form of generalized neuropathy in developed countries. For this reason, the simplified term “diabetic neuropathy” is commonly used. It is a polyneuropathy because of the diffuse damage to all peripheral nerve fibers; motor, sensory and autonomic. The sensory function is in particular affected, occurring insidiously and progressively, with characteristic stocking and glove distribution.

Autonomic neuropathy may cause postural hypotension, vomiting and diarrhea, bladder paresis, sweating abnormalities, impaired light reflex, impotence and retrograde ejaculation. Abnormal heart rate responses and prolonged QT intervals have been associated with increased risk of sudden death (27). The epidemiology and natural history of neuropathy is not well established but may be caused by microangiopathy and increased permeability of the capillaries that supply the nerves (8).

6.2b Macrovascular complications

Include systemic atherosclerosis affecting the large arteries resulting in cardiac vascular disease (CVD), peripheral vascular disease and stroke. In diabetes there is accelerated atherosclerosis, the severity is greater and the age of onset is earlier than in non-diabetic patients (8). Both cardiovascular mortality and morbidity are increased in T1D (33;37). T1D tenfold increases the risk of CVD (33), including the risk of myocardial infarction caused by coronary artery disease (38).

The etiologic factors of the increased risk of atherosclerosis in T1D are not fully understood. Traditional risk factors can only partly explain this. In T1D poor glycemic control, measured by HbA_{1c}, is a predictor of long term complications (39). Intensive diabetes therapy has long term beneficial effects on the risk of CVD in patients with T1D (20).

Part 2: Our project

7. Aims

Our thesis is part of a larger project where the aim is a global comparison of different strategies towards implementing internationally agreed guidelines in clinical practice. Our group consists of 12 students going to different parts of the world. To assess this subject, we used established guidelines for diabetes made by ISPAD and ADA. Many aspects of these guidelines are referable to other medical conditions as T1D is a chronic disease, acquired early in life, demanding lifelong treatment and with potential risk of serious complications. In our thesis the aim is to explore and discuss the challenges in implementing guidelines at two hospitals in USA and one in Norway.

8. Methods

We made an electronic questionnaire based on the 2009 ISPAD's and ADA's guidelines. The questionnaire was designed to collect information about T1D in children less than 15 years of age. The questionnaire consists of two parts. The macro part is designed to map the conditions within the country/state with questions regarding incidence, prevalence, mortality, national health, patient organizations, diabetes register and complications. In the micro part we look at how things are done at the local hospital/facility. Health personnel in the different facilities were interviewed in a semi-structured way. The interviews were tape-recorded because many of our questions were qualitative. We visited Children's Hospital of Orange County (CHOC) in California, University of Minnesota Amplatz Children's hospital in Minneapolis (U of M) and Ullevål University Hospital (UUH) in Oslo. In these hospitals we observed clinical practice in addition to the interviews. In Minneapolis we also had the pleasure of participating in a diabetes camp for youths, arranged by ADA.

9. Guidelines for treatment of diabetes

There are different sets of guidelines concerning pediatric diabetes. During this study we have been in touch with two of them; ISPAD and ADA. This is a presentation and comparison of the 2009 guidelines, which our questionnaire is based upon.

ISPAD is a professional international organization whose aims are to promote clinical and basic science, research, education and advocacy in childhood and adolescent diabetes. The members of ISPAD are scientific and clinical experts in childhood and adolescent diabetes. ISPAD has an evidence grading system for literature. They focus specifically on all types of childhood diabetes. The first set of guidelines from ISPAD was published in 1995 (40).

ADA is a U.S. organization working to prevent, cure and manage diabetes in the best way. The organization works for all people affected by diabetes. ADA Clinical Practice Guidelines are based on a review of the relevant literature by a diverse group of trained clinicians. ADA also has an evidence grading system for literature. The recommendations are revised on a regular basis and published in the journal *Diabetes Care* (41). In 2005, ADA published their first statement on the care of children and adolescents with T1D.

The **Diagnostic criteria for diabetes** in ISPAD and ADA are identical (Table 2). ISPAD and ADA both state that the **optimal care of pediatric patients with T1D** is by a multidisciplinary team of specialists trained in the care of children with pediatric diabetes. The recommended health professions included in the team should be trained in pediatric diabetes. If the latter is not possible to fulfill the care should at least be provided by health care providers trained and experienced in childhood diabetes. The ADA has a certification program available to become certified diabetes educators. ISPAD states that the team should consist of pediatrician specializing in diabetes or endocrinology (or physician with a special interest in childhood and adolescent diabetes), diabetes nurse specialist or diabetes nurse educator, dietician (or nutritionist), pediatric social worker with training in childhood diabetes and chronic illness and/or psychologist trained in pediatrics and with knowledge of childhood diabetes and chronic illness. According to both sets of guidelines, the recommended ongoing diabetes care should include: a **care visit every 3 months** for a re-evaluation

of diabetes management and review of home management records, an **annual visit** with greater attention to dietary assessment, laboratory screening, educational updates and psychosocial needs, long term complication screening and screening for comorbidities, and a **planned transition** to adult diabetes care which improves outcomes and helps to ensure continuity of care during this critical time. The guidelines recognize that the age of transfer to an adult clinic will vary according to individual and local circumstances.

Glycemic control is monitored through SMBG and HbA_{1c}. SMBG is the finger-pricks performed by the patient or caretaker at home several times a day. It helps to monitor immediate and daily levels of glucose, to determine insulin requirements and adjustments, detects hypoglycemia, and assists in management of both hypo- and hyperglycemia. ISPAD aim of collecting data on glycemic control from each diabetes center to compare with local, national, and international standards to quality assure and improve performance and standards of the diabetes care teams. The ISPAD goal for glycemic control is independent of the patients' age while the ADA guidelines' goal is dependent (Table 4). ADA base the less stringent goals in younger children on the fact that most children less than 6 or 7 years of age have a form of hypoglycemic unawareness and their counter regulatory mechanisms are immature. In sum this places them at a greater risk for severe hypoglycemia and its sequelae. ISPAD's recommendation is based on the Diabetes Control and Complications Trial (DCCT) which found that patients in the intensive treatment group had reduced risk for retinopathy compared to the conventional group even with the same HbA_{1c} (42). The DCCT study also found that 5-7 years of poor glycemic control even during adolescence or young adulthood increases the risk of chronic complications in the following 6-10 years.

Table 4: Goals for SMBG according to 2009 ADA and ISPAD guidelines, values in mmol/L* (mg/dL).

	ADA			ISPAD
	0-6 years	6-12 years	13-19 years	All age groups
Before meals	5,6-10,1 (100-180)	5-10,1 (90-180)	5-7,3 (90-130)	5-8 (89-143)
Bedtime	6,2-11,2 (110-200)	5,6-10,1 (100-180)	5-8,4 (90-150)	6,7-10 (120-179)
Overnight	6,2-11,2 (110-200)	5,6-10,1 (100-180)	5-8,4 (90-150)	4,5-9 (80-161)

*To convert mg/dL to mmol/L, multiply by 0.056. Vice versa, divide by 0.056.

The **frequency of SMBG correlates with glycemic control**. ISPAD recommend monitoring 4-6 times a day, while ADA's guidelines say at least 4 times a day.

Table 5: The recommended frequency of HbA_{1c} -monitoring per year according to 2009 ADA and ISPAD guidelines.

	ADA	ISPAD
Minimum	2	1
Ideally	-	Younger children: 4-6 Older children: 3-4
If changed therapy OR not meeting glycemic goals	4	-

Table 6: Target HbA_{1c} goals* according to 2009 ADA and ISPAD guidelines.

Years	ADA	ISPAD
0-6	<8,5% (but >7,5%)	<7,5%
6-12	<8%	<7,5%
13-19	<7,5%	<7,5%

* Require minimal levels of severe hypoglycemia and absence of hypoglycemia unawareness. If the latter requirement is not fulfilled, the glycemic targets must be increased until this is restored.

Both guidelines acknowledge **intensive insulin regimen** (basal-bolus regimen or insulin pump) as the best available option to mimic normal physiology and at the same time aim for optimal glycemic control. Prandial insulin should be matched to carbohydrate intake, pre-meal BG and anticipated activity. Insulin analogs are the recommended choice of insulin type. The DCCT clearly showed that intensive insulin therapy was a key part of improved glycemic control and better outcomes (20). Insulin pump therapy is at present the best way to imitate the physiological insulin profile. Insulin is infused subcutaneously at a pre-programmed basal rate and boluses are added to counterbalance the intake of carbohydrates. Both ISPAD and ADA recommend **carbohydrate counting**.

Ketoacidosis and monitoring of urinary or blood ketones: Ketones are determined in urine or blood. Blood ketone determination has been shown to be most helpful in avoiding emergency room visits. ISPAD recommends that ketone testing should be performed during illness with fever and/or vomiting, when BG value above 14 mmol/L (250 mg/dL) in an unwell child, when the BG levels are persistent elevated and when there is persistent polyuria with elevated BG or urine glucose, especially if abdominal pain or rapid breathing is present.

Table 7: Biochemical diagnostic criteria for ketoacidosis according to 2009 guidelines for ADA and ISPAD.

	ISPAD	ADA
Blood glucose	>11 mmol/L (≈200 mg/dL)	14 mmol/L (>250 mg/dL)
Venous pH	<7.3	<7.3
Ketones	Ketonemia or ketonuria	Ketonemia or ketonuria

Screening for micro and macrovascular complications and associated autoimmune

conditions. The guidelines have mainly identical screening programs for autoimmune diseases. The difference relates to time, i.e. when to perform the screening.

Table 8: Screening program for T1D-associated diseases according to 2009 guidelines for ADA and ISPAD.

	When to perform screening		Screening methods
Thyroid function	ADA	If clinical thyroid dysfunction is suspected. In an individual who has thyromegaly. Consider rescreening every 1-2 year.	Circulating TSH Free T4 Autoantibodies (if indicated)
	ISPAD	At diagnosis and, thereafter, every 2 nd year in asymptomatic individuals without goiter or auto antibodies. Otherwise more frequent.	
Celiac disease	ADA	At diagnosis of diabetes. Subsequently if symptoms occur. Consider periodic rescreening if negative antibodies.	Normal IgA levels AND elevated Tissue transglutaminase (tTG) antibodies OR elevated endomysial autoantibody (EMA)
	ISPAD	At diagnosis and then annually for 5 years. Every 2 nd year thereafter.	

Table 9: Screening program for macrovascular disease according to 2009 ADA and ISPAD guidelines.

	When to commence screening?		Screening methods
Dyslipidemia	ADA	If positive or unknown family history at age > 2 years, Otherwise at 10 years of age	Lipid profile every 5 years, or annually if abnormal results
	ISPAD	After age 12	Lipid profile every 5 years
Hypertension	ADA	-	Blood pressure annually
	ISPAD	-	Blood pressure annually
Foot care	ADA (General ADA guidelines)	Annually at least in adults	Inspection, assessment of foot pulses, and testing for loss of protective sensation
	ISPAD	-	-

Table 10: Screening program for microvascular diseases according to 2009 ADA and ISPAD guidelines.

	When to commence screening?		Screening methods
Retinopathy	ADA	Annually from age ≥ 10 years with 3–5 years duration	Ophthalmologic examination
	ISPAD	Annually from - years 11 with 2 years duration - 9 years with 5 years duration	Fundal photography OR mydriatic ophthalmoscopy (less sensitive)
Nephropathy	ADA	Annually from age 10 years with 5 years duration	Urinary albumin/creatinine ratio
	ISPAD	Annually from -age 11 with 2 years duration -age 9 with 5 years duration	Urinary albumin/-creatinine ratio OR first morning albumin concentration
Neuropathy	ADA (From the general ADA guidelines)	1) Distal symmetric polyneuropathy (DPN) annually from diagnosis. 2) Autonomic neuropathy 5 years after diagnosis.	1) DPN: tests such as pinprick sensation, vibration perception (using a 128-Hz tuning fork), 10-g monofilament pressure sensation at the distal plantar aspect of both great toes and metatarsal joints, and assessment of ankle reflexes. 2) Autonomic neuropathy: History and physical examination
	ISPAD	No recommendations	History and physical examination

Part 3: Clinical part

10. Hospital presentation and diabetes camp

10.1 Ullevål Hospital, UUH

Is part of the Oslo University Hospital (OUS) since 2010. Located in Oslo, the capital of Norway, and affiliated with the Faculty of Medicine, University of Oslo. Oslo is the largest city in Norway with 575 475 of Norway's 4.8 million inhabitants (01.01. 2009). The major ethnicity in Norway is non-Hispanic White. At the end of 2009 11,4% of the population in Norway were of immigrant background; 46,6% from Europe, 36,1% from Asia, 12,2% from

Africa, 3,3% from South- and Central-America and 2% from North-America and Oceania. In Oslo 27% of the population are of immigrant background (2009)(43). Norway is several times ranked on top in the Human Development Report by United Nations Association. The life expectancy in 2008 was 81 years for both sexes. UUH used to be Norway's largest hospital, with a staff of around 9,500 treating more than 620,000 patients yearly. OUS is a specialized hospital in charge of national, regional and local hospital assignments (44). OUS is the Norway's leading emergency hospital. The hospital is responsible for a major part of all medical and healthcare research conducted at Norwegian hospitals and a significant proportion of training of health care personnel in Norway. The **Pediatric center** at Ullevål is Norway's largest clinic for children. The functions include emergency department, general pediatrics, children surgery and intensive treatment for neonates, toddlers and children (45). We visited the endocrine outpatient clinic at UUH in 2009. The questionnaire this thesis is based on

Figure 8: Map of Northern Europe and Norway.



was evaluated after several test interviews with diabetes nurse Siv Janne Kummernes and consultant in pediatrics, Torild Skrivarhaug. We have also observed consultations with children with T1D at the outpatient clinic.

10.2 Children's Hospital of Orange County (CHOC)

CHOC is situated in the city of Orange in California, on the west coast of the U.S, close to Los Angeles. California is the heaviest populated state in the U.S, and the third largest by land-area. In 2009 41,7% of the population were non-Hispanic White, 37 % Hispanic or Latino origin, 12,7% of Asian origin and 6,6% were Black (46). The official language in California is English. In 2005 however, 28.2% spoke Spanish as their first language, while 57.6% had English as their first language.

In 2007, the gross state product was about \$1.812 trillion, the largest in the U.S. California is responsible for 13 % of the United States gross domestic product. CHOC is a private hospital with 238 beds distributed on different wards. It is affiliated with the University of California, Irvine. CHOC provides inpatient and outpatient pediatric specialty care to patients. The hospital's functions are intensive treatment for neonates, toddlers and children, general pediatrics, surgery, neuroscience and oncology. CHOC also includes many primary and specialty care clinics (47). The number of beds the diabetes clinic has access to in the hospital is approximately 80. We followed the daily routines at the endocrinology outpatient clinic at CHOC for two weeks in July 2009. During our stay we observed how they work with children with diabetes, from newly diagnosed patients at the hospital to patients with a long history of T1D in the outpatient clinic. We participated in consultations with the doctors and nurses, and at the group-organized education. We interviewed Dr. Mark Daniels, consultant in pediatric and endocrinology at CHOC. Many of our questions were answered through observation at the hospital.

10.3 University of Minnesota Amplatz Children's hospital (U of M)

Located in Minneapolis, the capital of the state of Minnesota, and affiliated with the University of Minnesota Medical School. Minnesota is located in Midwestern U.S. It is the 12th largest state and the 21st most populated with 5.3 million inhabitants. In 2009 84.8% of the population was non-Hispanic White, 4.3 % Hispanic or Latino origin, 3.8% of Asian origin and 4.7% were Black (48). The metropolitan center in the state is the twin-cities, Minneapolis and St. Paul, where 60% of the

population lives. Minnesota ranks among the healthiest U.S. states with a high percentage of literate people.

The University of Minnesota Amplatz Children's hospital provides a wide range of pediatric programs and services (49). University of Minnesota Amplatz Children's hospital is ranked by U.S. News & World Report among the best children's hospitals in the U.S. for treating diabetes and endocrine disorders. The hospital is the leading clinical site for TrialNet, an international network of clinicians working to improve the knowledge of T1D (50).

Figure 9: Map of USA.



We participated in the daily work at the endocrinology outpatient clinic in Minneapolis for one week in August 2009. During our stay we learned how they work with children with diabetes in the hospital and in the outpatient clinic. We participated in consultations with the doctors and nurses and joined a fund raising in Fairview amusement park. We interviewed the diabetes nurses Anne E Jackson and Shannon Beasley and also got some questions answered by Dr. Toni Moran, consultant in pediatric and endocrinology. Many of our questions were answered through observation at the hospital.

10.4 Diabetes camp

The patients at all the hospitals we visited are offered to attend summer camps organized by non-profit organizations. At UUH these camps are organized by the Norwegian Diabetes Association (NDA), at CHOC both Pediatric Adolescent Diabetes Research Education (PADRE) and ADA arrange camps for children with diabetes and at U of M ADA arrange these camps.

During our stay at the U of M, we had the pleasure of joining the staff at Diabetes Camp. Children with diseases might not have access to regular camps because of lack of accept from the organizers, or the parents not allowing them because of fright for their health. Diabetes camp is an option for these children. These camps are held during the summer holiday and are popular for children and adolescents; they meet peers, make friends and do fun activities.

Diabetes camp has medical staff and volunteers trained in diabetes. All participants have diabetes. At diabetes camp, children with diabetes experience that they are as other children. They learn to be in activity without fear and to eat the same food as everyone else. They understand that from the outside, it is impossible to tell if anyone has diabetes.

We visited Camp Needlepoint arranged by the ADA. The camp lasts for one week in August, and is held at the YMCA Camp St. Croix, Hudson Wisconsin. The age range of this particular camp is 8-16 years. For the children aged 5-9 years a day camp is held. All the camp participants have diabetes, most of them T1D but some have T2D. Most children are attending alone, but some have their parents there as volunteers. The camp aims to encourage independence and self-management with appropriate medical supervision to ensure the best possible experience for every camper. In advance the children choose what activities they want to participate in, like canoeing, sailing, rock climbing and hiking.

At check in, parents inform the medical staff about their child's typical daily activity level, experiences from previous camps or anticipated changes to insulin doses or pump settings.

The children were divided into different groups that should be together for the whole week, living together in a camp cottage. The groups consisted of 10 boys or girls at the same age. The group leaders were two adolescents, 17 years or older, most of them had T1D and had participated in the camp earlier. Every group had daily supervision by the medical staff for insulin dosing.

The medical staff is a mixed group of health professionals. All of them are licensed in the state where the camp is held. The majority are also involved in diabetes care in their local community on a year-round basis.

The medical staff was in touch with their groups before every meal (breakfast, lunch, dinner and evening snack) to help the children adjust insulin. The children had to choose from a menu and plan their food intake. Then they did the carbohydrate counting together with the medical staff, measured their pre-prandial BG and based on this the medical staff adjusted the insulin to dose. Most of the children were on multiple injections therapy while some were on pump therapy. First priority at camp is not perfecting BG management but rather the safety for every camper (51). The medical staff, volunteers and group leaders were carrying with them glucose monitoring strips, glucose meters, sugar tablets, sugar gel and glucagon at all times.

The group leaders had guidelines regarding how to act on low and high BG. This included overnight monitoring if some of the campers had low BG in the evening.

The ADA does their best to keep the camp fee as low as possible for families. Through year-round fundraising efforts and donors, they manage to charge families only 50% of the true cost to provide camp for a child (52). In addition, camperships are available to help families that cannot afford the camp fee.

11. Results

In our questionnaire we wanted information about children less than 15 years. This was partly available at UUH, the rest of the information we collected includes children up to 18 years.

11.1 Diagnostics

In all the hospitals we visited the classical symptoms that make the patient and his or her parents contact a doctor are excessive urination, increased thirst and fatigue. If the patient is sick for a long time they see weight loss as well. All hospitals adhere to guidelines; in Minneapolis and CHOC they follow ADA, at UUH they follow national guidelines which are similar to ISPAD. ADA and ISPAD guidelines concerning diagnostic criteria are similar (Table 2). The diagnostic criteria for DKA are according to ISPAD/ADA in all the hospitals (Table 7). All the hospitals have access to interpreters when needed.

Table 11: New onset T1D.

New onset diabetes	CHOC	University of Minnesota	UUH
New onset T1D in 2008 (n)	110	97	33
DKA at diagnosis (%)	20-25	< 15	25
Average time of hospital stay at diagnosis (days)	2	None. They are treated at out-patients-clinics	11
Who set the diagnosis	General practitioner	General practitioner	The hospital staff

Ullevål University Hospital

The diagnosis is set by specialized health service. All patients with newly diagnosed T1D are admitted to hospital. The length of the stay depends on the patient's situation at home, including how fast the child and caretakers learn to deal with the diabetes and how safe they feel around the administration of insulin, measuring of BG etc. About 25 % of the patients have DKA at diagnosis.

Children's Hospital of Orange County

The diagnosis is most often set by the general practitioner (GP), if not by specialized health service. All children with newly diagnosed T1D are admitted to the hospital, regardless of their condition.

About 20-25 % of the children have DKA at diagnosis. The hospital is only for children, but they have an adolescent clinic run by physicians who usually work at the endocrine clinic.

University of Minnesota

The diagnosis is most often set by the GP. Newly diagnosed patients are managed in the out-patient clinic unless they have DKA. If the patients have DKA at diagnosis they are most often 2-3 days in the intensive ward. Minneapolis was the hospital we visited with the least percentage of DKA amongst new onset T1D.

11.2 Treatment and follow-up at diagnosis

In all the hospitals the child and its family and caretakers are educated at diagnosis. This education is individual. The doctor gives some basal information about the disease, and then a diabetes educator shows them how to measure BG, inject and draw insulin into the syringe and operate the insulin pens or the insulin pump dependent on the choice of injection device. They also learn about hypo- and hyperglycemia and how to handle this. Carbohydrate counting is used systematically from day one at all the hospitals. The children and family meet a nutritionist and learn about nutrition, healthy food and food in relation to T1D. They also learn about the amount of carbohydrate in different kinds of food, and the effect it will have on the BG. All children are recommended to eat healthy and to have a diet composed of many different kinds of nutrients. The need for a diet depends on the treatment regimen chosen, and this differs in the different hospitals.

Ullevål University Hospital

All children with T1D are managed at the hospital in the outpatient clinic, nobody are followed up by their GP. In 2008, approximately 300 patients were followed up at UUH. Responsible for the education at diagnosis is the nurses on the ward and the doctor. The nurses on the ward are specially trained to be able to do this education. During the hospitalization the patient meet all of the professions in the multidisciplinary team (discussed in “Follow up”) in separate appointments. The social worker can help the family with the rights and different funding arrangements which they can claim. After discharge from the hospital the family will have a new appointment in one week and daily phone contact if needed. Next appointment will be in two weeks, four weeks, two months and then every third month.

Children's Hospital of Orange County

1100 patients with T1D are followed up at CHOC in the out-patient clinic. Because the children at CHOC get two shots of insulin a day, they need to be on a diet to keep the BG within target range. The nutritionist helps the family to compose meals based on what the child usually eats. The amount of carbohydrates must be about the same every day, but the child can get “free food” whenever wanted. This is food that won't raise the BG, for example vegetables and meat. The social worker meets with every new patient. After discharge the family will have daily phone contact with a diabetes nurse at the clinic for approximately two weeks. They tell the BG values and are guided in the insulin dose in relation to food for the next 24 hours.

The following Monday all children diagnosed during the past week are invited to reeducation with their parents. This is a group education, all the information from the day of diagnosis is repeated and questions are answered. The parents and children are separated. One month after diagnosis is the first appointment in the out-patient clinic, then every third month.

University of Minnesota

250 children with T1D are followed up at the out-patient clinic. When the diagnosis is set, the family returns to the clinic after one or two days, then one week, three weeks, a month after diagnosis and thereafter every third month. Often the information is the same at every consultation but handed over to different family members or caretakers. The families are on daily base in contact with the diabetes nurses, even by e-mail or phone, for the first two weeks. The nurses tell them how to adjust the insulin and after two weeks most of them have an understanding of diabetes and how the boluses are adjusted.

11.3 Follow up

At all the hospitals there is a multidisciplinary team who is responsible for the treatment and follow-up of children with T1D. In the team there are doctors, diabetes nurses, psychologists, nutritionists and social workers. Children attend diabetes health checkups every third month if everything is going well with the child, if not the frequency is increased to once per month. At all the hospitals more than 90% of the patients attend their appointments.

Ullevål University Hospital

The children are followed in the clinic until they are 18 years. The nurses and doctor are responsible

for the continuous follow up. The psychologist, social worker and nutritionist are called if needed. The child has one particular contact person, a doctor. The nurses are part of a team, so each patient can meet different nurses at each checkup. In Oslo the school nurses are very little involved in the care of children with diabetes. One school nurse is working at 4-5 schools, so it is not sufficient time to follow up the children with diabetes.

At the regular checkups the patients see a diabetes nurse and the doctor every time. In addition the diabetes nurses are available on the phone and can arrange meetings if the patients need help or guidance between the regular checkups. Many “everyday problems” are solved over the phone. If the patients cannot attend to an appointment they usually cancel in advance. There are no special characteristics of the patients not attending their appointment, but most of the cancellations are appointments with the nurse, not the doctor.

Children's Hospital of Orange County

The children are managed in the pediatric department until they are 18 years if the parents have insurance. Most private insurances make the children go to adult physicians when they are 18 years. If the children don't have insurance, they are managed at CHOC until they're 21.

The diabetes nurse and the doctor see the patient at every checkup. The nutritionist and the social worker are called in whenever there is need. Once a week there is a state health insurance clinic at CHOC, this day the social worker is always present. Every month the clinic has meetings where the focus is on patients with more special problems; psychology, social circumstances and behavioral problems. These subjects are discussed between the doctor, nurse, psychologist and social worker.

On average there is one nurse per three or four schools in California because of financial problems. The only people who are allowed to give insulin at school are the school nurse, the child itself and the parents. No one else can give insulin at school. The hospital claims that this is some of the reason why children in school age are on a two shot-regimen (Figure 10). This way the children don't have to take insulin at school.

At CHOC they have no method for tracking the patients that do not attend their appointments. The prescriptions last for one year at the time, and the physicians won't give new prescriptions if the patients don't show up to their checkup. There are no special characteristics of the patients not

attending their appointments. At CHOC the children don't have one particular contact person, it's a team approach.

University of Minnesota

The patients are followed in the clinic until they are 18 years or through college (up to 22-24 years depending on the college). When they're embarking on the adult life they have to go to an adult clinic. The reason for this is that most parents' health insurance plan will cover the children through college.

We have no information regarding school nurses in Minnesota.

The continuous follow-up is by a doctor and a nurse. The nutritionist and the psychologist are available when needed. All patients have a set contact person responsible for the follow-up at the hospital, this person is a nurse. The hospital claims that the characteristics of the patients that do not attend their appointments are low socioeconomic status.

11.4 Education and reeducation

The reeducation in all the hospitals is a continuous process based on individual needs. At UUH and CHOC some of the education is organized in groups.

Ullevål University Hospital

Most of the education at UUH is individual. Twice a year they have a course where all the patients that have been diagnosed during the last 6 months are invited to reeducation together with their parents. Once a year all children who turn 12 years the same year are invited to reeducation. This is a group education where they go through all the aspects of diabetes again, and the children are encouraged to get more involved in their own treatment. The parents do not attend to this reeducation; it is only for the children.

Children's Hospital of Orange County

At CHOC they have a combination of individual and group education. PADRE, a non-profit organization in California, organizes the group education. They get their funding through donations and fundraising. It is the physicians at CHOC who identifies the needs, and then PADRE does the education. The nurse educators are employees at CHOC, but they get paid by PADRE. Nurse educators can also have lessons for teachers and activity leaders/coaches if they wish to learn more about diabetes.

University of Minnesota

All education at the clinic is individual. The clinic does not consider it efficient to educate families together because the need for information is very different for younger versus older kids. Occasionally the nutritionists have educated group wise because carbohydrate counting is the same regardless of the patient's age. There is a set curriculum for re-education, but it is not age dependent and is done continuously. The clinic is working on a webpage for patients and their relatives. This net clinic was developed in 2008 for the purpose of reeducation. As an example the parents can search the net clinic for information if they forget what to do on sick days. The webpage contains reeducation, information about diabetes and the patients can post their own experiences. It is also a possibility to e-mail the diabetes nurses via the net clinic. At least once a year the clinic tries to do an educational program where they invite all their patients to attend. Usually the doctors will talk about research and where they are about a cure for diabetes. The diabetes educators also talk about an educational topic. Unfortunately, few patients attend these events.

11.5 Parental involvement

At all the hospitals the parents are asked to involve in the treatment. The degree of parental involvement depends on how much they want to involve, and how much the children let them.

Ullevål University Hospital

The children can attend their appointments without parents, this happens often as the child grows older. However, the diabetes team still wants to involve the parents; as a minimum they must attend one appointment per year together with their child. If the child is not doing well with the diabetes, the parents are always asked to get involved.

Children's Hospital of Orange County

All children under 18 years have to come with their parents to the checkups. Parents are asked to always be aware of the children's BG, and to observe when they do their shots and measure their BG.

University of Minnesota

The parents are always present at the consultations until the children are 18 years. Parents are kept involved in the treatment and follow-up, but the degree is age dependent. If needed, the teenagers are talked to individually.

11.6 Alcohol/Contraception/unintended pregnancies

None of the clinics consider drug or alcohol abuse to be a bigger problem among children with T1D than in the general population. The hospitals do not have routines for when to talk about alcohol and drug abuse, this is up to the doctor and nurse. Unintended pregnancies are not a frequent problem at any of the hospitals. The importance of contraceptives and the impact T1D will have on the pregnancy is discussed.

Ullevål University Hospital

At UUH they try to talk about these subjects as early as possible, when it is appropriate. At the reeducation for the 12-year olds they bring up alcohol and the effect it has on the BG. Most of the doctors talk routinely about sex/contraceptives and the impacts of alcohol on diabetes. Occasionally the doctors prescribe contraceptives, but usually this is done by the GP. Dr. Torild Skrivarhaug at UUH has never experienced unintended pregnancies among the patients.

Children's Hospital of Orange County

Alcohol-education is organised through PADRE as group education. Contraceptive counseling is not done systematically because it is not a routine. However, the physicians try to bring it up when the patient is in a childbearing age. Dr. Mark Daniels knows about 6 girls who got pregnant the last couple of years. He claims that the characteristics of these patients are lower socioeconomic status, but more important is that they are in poor control of their diabetes.

University of Minnesota

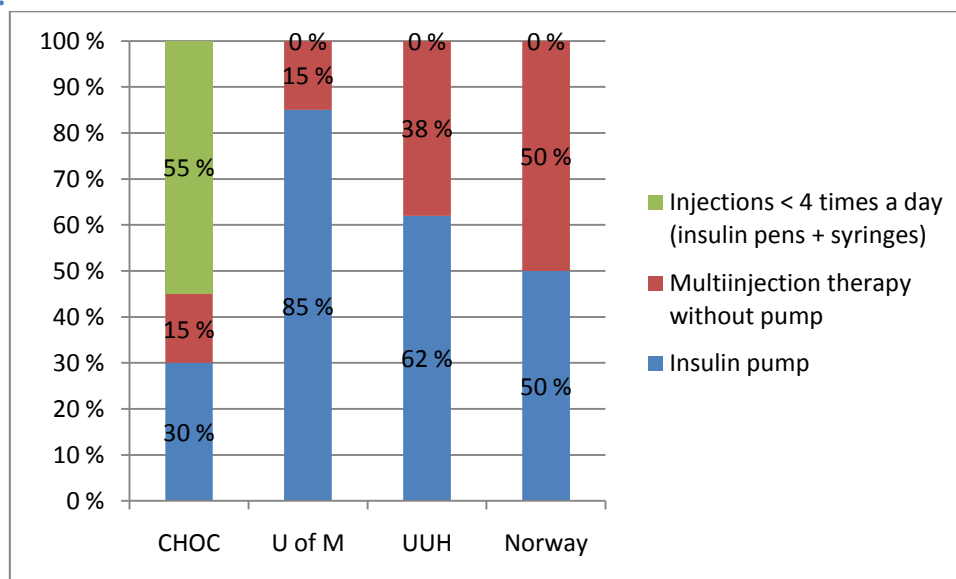
Before college (the age of college start is 18 years) the clinic routinely do a talk about sex and the impacts of alcohol consumption on the diabetes. The girls are informed about contraception. The clinic thinks they are talking about this too late. If the suspicion is raised about sex and alcohol before college the doctor will discuss the subject at an earlier stage. During the last 10 years the clinic has experienced 2-3 unplanned pregnancies among their female patients in college, and two of their male patients have made girls pregnant. The hospital claims the characteristics of these patients are low self-esteem.

11.7 Medical treatment

Table 12: Proportion of patients with T1D on different injection devices at the visited hospitals.

Proportion of patients on different injection devices	CHOC	U of M	UUH	Norway
Syringes (%)	52.5	0	0	0
Insulin pen (%)	17.5	33	38	50
Insulin pump (%)	30.0	67	62	50

Figure 10: Proportion of patients on different treatment regimens for T1D at the visited hospitals.



The proportion of patients on the different treatment options in the different hospitals are illustrated in figure 10. All hospitals use only insulin analogues. None of the clinics use premixed insulin preparations. At all the hospitals, the patients on multi-injection therapy use long acting insulin (Lantus or Levemir=Detemir) and short acting insulin (Novolog=NovoRapid or Humalog). The choice of insulin analogues varies between the hospitals. Continuous subcutaneous glucose monitoring (CSGM) is available for loan at all the hospitals. It is the doctor or nurse who recommends patients to use CSGM.

Ullevål University Hospital

All new onsets are offered to start with the insulin pump and around 98% of the patients accept this treatment. The patients not on pump use insulin pens (Table 12).

There are no different strategies for insulin therapy concerning the child's age. All new onsets use the pump, this is especially important if the child is very young (less than 6 years) because they often need very little insulin, especially in the honeymoon-phase and it is easier to give diluted insulin through a pump.

If the child gets acutely ill they usually call the Emergency Room (ER). If it happens during the day they can call the diabetes team or outpatient clinic. This way they can prevent an episode of DKA from emerging. Just after diagnosis the patient can call the ward and get help there.

Children's Hospital of Orange County

All children start on a two-shot regimen. At CHOC most patients use syringes for insulin injections (Table 12). The reason why the clinic prefers syringes above pens is the flexibility they provide concerning combination of insulin types. This way the patients can do the injection of both long- and short-acting insulin in one shot. They use short acting insulin plus intermediate-acting insulin in the morning to cover breakfast, lunch and mid-day snack. The shot in the afternoon is short acting insulin plus long-acting to cover dinner and the whole night.

There are different strategies for insulin therapy concerning the child's age. Under the age of 5 years and over the age of 14 years they tend to use multi injection therapy and pumps. Children in school age tend to be on a two-shot regimen partly because they want to do as few injections as possible, and partly because there aren't enough nurses at the schools to give insulin during the school-day.

If the child is acute ill from their diabetes they call the clinic, the parents are asked not to go to their GP. If the problem can't be solved over the phone, the patient with its family goes to the ER.

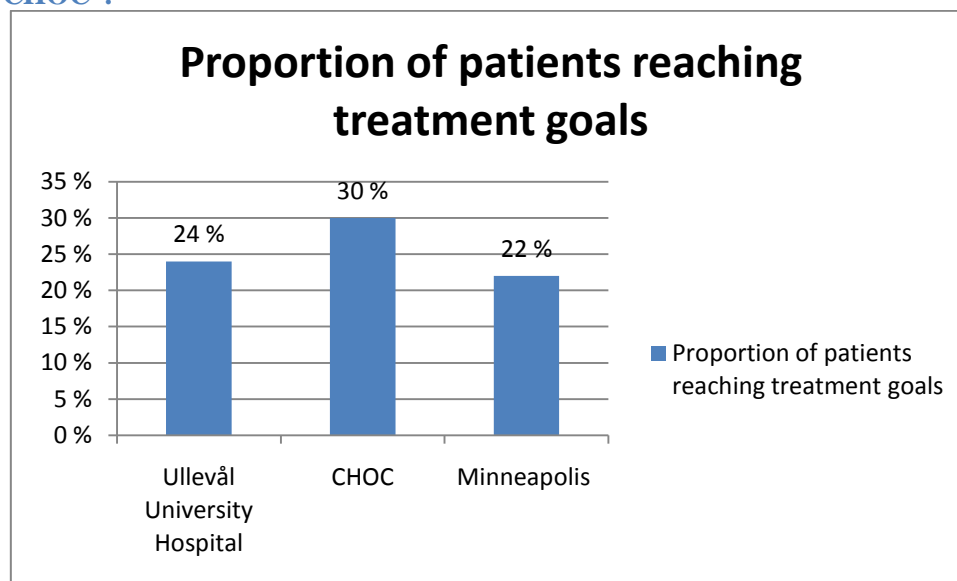
University of Minnesota

All patients start on pens and are offered a planned transition to insulin pump. The patients not on pump are on the basal bolus regimen. There are only a handful of the patients on mixed insulin (75:25 insulin types). Intermediate-acting insulin plus Rapid-acting insulin were not used. There are different

strategies for insulin therapy according to the child's age. The toddlers are more frequently started on insulin pump. With a pump it is possible to dilute down the insulin to get better control, this way the youngest children can be more stable on a pump. Another benefit with pumps is that it is easier to deliver the insulin in a pump than through injections, and they can stop the pump when the BG is low.

11.8 Treatment goals

Figure 11: Proportion of patients reaching treatment goals for HbA_{1c} in 2008. Goal in Minneapolis and UUH was <7,5%, while varied between 7,5% and 8,5% depending on age group at CHOC*.



*The number for CHOC is an estimate done by Dr. Mark Daniels, Consultant in Pediatrics and Endocrinology at CHOC.

All the hospitals follow guidelines for treatment goals (Table 6). At UUH National guidelines for treatment goals are adhered to; these are based on ISPAD's guidelines. In Minneapolis the ISPAD guidelines are adhered to, while CHOC adhere to ADA guidelines. All the hospitals register the number of patients reaching their treatment goal for HbA_{1c}. At UUH they keep a database for patients achieving their treatment goals, they also report this to a national register; The Norwegian Childhood Diabetes Registry. At CHOC Dr. Mark Daniels gave us an estimate, not the exact numbers of patients achieving their treatment goals. In Minneapolis they keep a database of their patients with HbA_{1c} >10% and <7,5%. Annually the clinic sends a report to ADA. This is a part of the hospitals accreditation. The average HbA_{1c} in 2008 at UUH was 8,68%, at U of M it was 8,3%. We do not have this information from CHOC. Other treatment goals at all the hospitals are proper/normal growth and

development in the pediatric patients, and absence of episodes of severe hypoglycemia and DKA.

11.9 Screening for autoimmune diseases and late complications

All the hospitals had a routine screening program for autoimmune diseases and late complications (Table 13 and 14).

Table13: The screening for associated diseases performed at the visited hospitals.

Screening for autoimmune diseases	CHOC	U of M	UUH	Norway
Celiac disease	Every 3 or 4 year, more frequent if symptoms	Annually	Annually	Annually
Hypo-/hyperthyroidism	Annually	Annually	Annually	Annually

Table 14: The performed screening for late complications at the visited hospitals.

Screening program for late complications	CHOC	U of M	UUH	Norway
Retinopathy	Annually 5 years after diagnosis	Annually after 10 years of age	Annually after 11 years of age and 2 years duration of diabetes or 9 years of age and 5 years duration	Annually after 11 years of age and 2 years duration of diabetes or 9 years of age and 5 years duration
Nephropathy (test for microalbuminuria)	Annually 5 years after diagnosis	Annually	Annually	Annually
Neuropathy	None	None	None	None
Hypertension	-	-	Annually	Annually

11.10 Acute and late complications

The proportions of patients with acute and long-term complications are shown in table 15 and 16.

UUH was the only hospital who had a local register, they also report their numbers to the Norwegian Childhood Diabetes Registry.

Table 15: Frequency of acute complications at the visited hospitals.

Acute complications	CHOC*	U of M**	UUH***	Norway***
Rehospitalisation with DKA (%)	< 1	4,3	4	5
Severe hypoglycemia with unconsciousness and/or convulsions (%)	5	7,9	9,4	6

*The numbers for CHOC is an estimate done by Dr. Mark Daniels, Consultant in Pediatrics and Endocrinology at CHOC. **Local Registry at U of M. *** The Norwegian Childhood Diabetes Registry.

Table 16: Frequency of long term complications at the visited hospitals.

Long-term complications	CHOC*	U of M**	UUH***	Norway***
Persistent micro albuminuria (%)	5-10 (Spot urine sample)	?	0,1	0,4
Nephropathy (%)	0	0	0	0
Neuropathy (%)	0	0	0	0
Retinopathy (%)	0	0	0	0,2
Hypertension (%)	5-10	1	3,3	

*The numbers for CHOC is an estimate done by Dr. Mark Daniels, Consultant in Pediatrics and Endocrinology at CHOC. ** The numbers for University of Minnesota is an estimate done by Dr. Toni Moran, Consultant in Pediatrics and Endocrinology at University of Minnesota. *** The Norwegian Childhood Diabetes Registry.

11.11 School, hobbies and sports

At all the hospitals, the main assistance the patient receives in relation to school, hobbies and sports is information and education.

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The nurses go out to schools and kindergartens and educate teachers/caretakers soon after the patients discharge from the hospital. The parents are always involved in this process. Often the parents have made a form where they tell the insulin boluses in relation to BG, and they are always available on the phone. Many children have cellphones. From 3rd grade the nurses go to the school and teach the patient's schoolmates about T1D. The parents have the responsibility to inform activity leaders/sport coaches about T1D. They receive assistance from the hospital in form of a brochure, in addition the coaches are welcome to contact the clinic. The hospital arranges some social happenings for the patients. Once a year they have a group for girls about 9-10 years old. The aim for these meetings is

that the patients can meet other children with T1D. The parents also discuss problems and experiences around having a child with diabetes. NDA arranges summer camps for children with diabetes.

Children's Hospital of Orange County

Every patient in school-age get a school-form, this is guidance for the personnel at school. If the school does not have experience with diabetes the hospital sends a nurse-educator to educate the staff. Nothing is done towards hobbies and sports. In California all social activities for children with T1D are organized through private or non-profit organisations, nothing through the state. PADRE arranges social activities for the children and their parents. This could be trips to amusement-parks, summer fairs, surf-day, Halloween-parties, summer camps etc.

University of Minnesota

The parents have the main responsibility for education of teachers, coaches etc. The clinic does not have capacity to go out to educate, but occasionally they organize educational meetings for school nurses and teachers at the hospital. Social activities arranged for the children and their parents are mainly through private or non-profit organizations, not through the hospital. The most important organizations in Minneapolis are ADA and The Juvenile Diabetes Day Research Foundation (JDRF). JDRF organize support groups; for mums, dads, young people, old people, teen agers, athletes, baby sitters club. The nurses at the clinic try to arrange some activities but the funding is missing. The clinic does not have a support group, its alternative way to funding is through medical companies. Support groups arranged by the hospital are few, but free for the patients because the drug companies support them.

11.12 Quality of life

At UUH and CHOC they are conducting research on the quality of life among children with diabetes, in Minneapolis this is not, and has not been done. In 2009 a large study on the quality of life in children with T1D was started at UUH; this project will keep on going in 2010. CHOC were in 2009 in a process where they looked at the attitude towards diabetes-care among adolescents. Depression is underdiagnosed among children with T1D (53). About 2% of the patients at CHOC are diagnosed with depression.

11.13 Overweight

At CHOC and in Minneapolis overweight (Body Mass Index (BMI) over 25) is not a bigger problem among children with T1D than in the general population. In general about 30% of the kids in USA are overweight. At UUH approximately 18% of the children with T1D are overweight, less than 1% has a BMI over 30. At all three hospitals the treatment is consultation with a dietitian and advice toward healthy diet and physical activity.

Ullevål University Hospital

About 30% of the overweight patients are older than 15 years old. There are no special characteristics about these patients; at UUH they don't register socioeconomic status. The children with overweight in general have a higher HbA_{1c} than the children of normal weight. Yet there are no analyses on the complication rates available, but these will come in a few years.

Children's Hospital of Orange County

Overweight is a little more frequent in the Hispanic population. The treatment regimens are not effective. Children with overweight in practice do not have significant more complications than children with normal weight. Depression is a problem related to overweight and T1D. A study done four years ago showed that children who were overweight scored the same on quality of life as children with cancer (53).

University of Minnesota

Overweight is related to ethnic groups and socioeconomic background. The prevalence of overweight is highest in "children of color" and in those with low self-esteem. The hospital's prevention and treatment plan is not effective. Dr. Toni Moran claims that there are no other problems related to children with obesity and T1D than to children with only obesity.

12. Discussion

Guidelines are important tools in the diagnostics, treatment and follow up of patients with chronic diseases. They help to manage the disease in a standardized and consistent way which is internationally acknowledged. Challenges regarding implementation are mainly economical and practical. The guidelines are made in the western part of the world where the availability of resources generally is of the better. We have visited hospitals situated in areas with good infrastructure and stable economy; therefore we cannot draw conclusions regarding possible economic challenges which are more frequent in countries of the third world. We did, however, also in our survey find modifications made for practical and economic reasons.

12.1 Diagnostics

The diagnostic criteria at the hospitals we visited were similar and adherent to the Guidelines of ISPAD or ADA. This finding illustrates broad agreement regarding the diagnostic criteria for T1D. The diagnosis of T1D can be highly suspected on symptoms alone, but to confirm the diagnosis, measurement of BG is necessary. In the western part of the world the equipment needed is easy to access, but the situation might be different in other parts of the world. We consider the diagnostic criteria in the guidelines to be relatively easy to implement in a clinical setting worldwide.

There was a difference between where newly diagnosed patients with T1D were treated the first time in the three hospitals we visited. There was also a variation between the average lengths of stay for the patients being admitted to the hospital at diagnosis (Table 11). ISPAD opens for outpatient management at time of diagnosis if satisfactory resources and knowledge is available. In all the hospitals we visited the resources were available. Nevertheless, only one of them chose this for their patients. The reason for this might be inadequate experience on outpatient management. Other possible reasons might be the hospitals opinion of what is best for the patient and the well-known fact that it is difficult to change procedures that are well functioning. In a global perspective we think that outpatient management of newly diagnosed patients with T1D will be difficult because of lack in knowledge and experience outside the specialized units. At all the centers, the symptoms that caused contact with the health services were the classical symptoms of T1D.

The diagnostic criteria for DKA were similar and according to guidelines at all the hospitals. The low proportion (table 11) of patients with DKA at diagnosis in Minneapolis could be explained by good knowledge of diabetes and its symptoms in the population, good economy, a relatively high incidence of the disease in addition to easy access to health care systems. However, if this is the reason we would expect the situation to be similar at UUH. The rates of frequency of DKA at onset of diabetes inversely correlate with the regional incidence of T1D. DKA at diagnosis is more common in children whose families do not have ready access to medical care for social or economic reasons (34).

12.2 Treatment and follow up

All the three hospitals had multidisciplinary teams available for the patients in accordance to the guidelines. This form of care is very unlikely to be available in areas with limited availability of resources and health care facilities, and where the rate of T1D is low. In many countries it is not possible to adhere to the guidelines because of economic reasons and lack of educated staff.

Interpreters were available in all the hospitals we visited. Both in USA and Norway this is a right according to the law of patient rights.

According to the guidelines, education could be organized individually or in groups. At UUH and in Minneapolis the education was mostly individual. At CHOC it was a combination. The hospitals' organization of the education was based on their opinion and previous experience. The number of newly diagnosed children each week is also part of the explanation. The education must be adjusted to every patient's social, ethnical and cultural background. Education is a continuous process that demands close follow up, this could be challenging in some parts of the world where access to health facilities is poor.

The way of administering insulin to the patients was especially discrepant between CHOC and the centers in Minneapolis and Oslo (Figure 10). The reasons for this were practical, economic and social. The guidelines recommend the insulin replacement therapy to be as close to the physiological insulin production as possible. Generally, this is best managed through the pump. Complications and treatment goals in multi-injection therapy is equal to the pump (54). In Minneapolis and Oslo the majority of the patients were on multi-injection therapy as recommended in guidelines, at CHOC approximately 50% of the patients were on multi-injection therapy (Figure 10). The reason for the

relatively high percentage on a two-shot regimen at CHOC was mainly the state's law which requires the presence of a school nurse to inject insulin at school. School nurses are employed at the minority of the schools. Another aim was to minimize the number of needle-sticks for the children.

At CHOC a large proportion of the patients used syringes (Table 12). It was stated that injections through syringes provide more flexibility than pens because they make it possible to combine different types and volumes of insulin in one syringe. This way, the number of injections needed is reduced. To draw insulin into a syringe seems more complicated than using a pen. This could result in fewer children being able to participate in the treatment, and could be part of the explanation for the high percentage on a two-shot regimen (Figure 10).

We found a difference in the proportion of patients on insulin pumps (Figure 10). Economy and education are important factors that could influence the use of pumps. In low-income countries this is not possible to fulfill. We would not expect economy to be a limiting factor at any of the hospitals we visited. In Norway the insulin pump is funded by the public health system and is therefore free for the patients. In Minneapolis most of the patients had insurances that covered the pump expenditure. At CHOC the patients also had insurances that would cover the expenditure related to pump therapy, but the staff had little experience on the treatment regimen and for this reason it was not their first recommendation. The patients had to ask for this treatment option.

All the hospitals mainly had patients on analogues as recommended in guidelines. This is possible because of the advanced economy in the countries we visited. Our findings might have been different in a country with a weaker economy since regular insulin is far cheaper.

Carbohydrate counting was used systematically at all the hospitals as recommended in guidelines. A prerequisite for this is education. A challenge in the use of this tool is the risk of making a strict diet based on the insulin dose and not adjusting insulin to food-intake. The impact on daily life will be larger if the diet is very rigid. The focus on nutrition, diet and weight can together increase the risk of developing eating disorders. The guidelines recommend varied nutrition intake where all the nutrients are present. In countries where the food availability and the affordable expenditure on food are limited this could be hard to accomplish.

12.3 Treatment goals

At UUH and in Minneapolis the ISPAD's guidelines for treatment goals are adhered to, at CHOC the ADA's guidelines are followed (Table 6). The goals stated in the ADA vary in different age groups, this makes the goals easier to accomplish for the younger kids where the glycemic goals are less stringent than the ISPAD's. The parents have the full responsibility for the treatment in this age group (less than 6 years) which usually has a positive effect on the outcome. On the other hand varying goals may be confusing for the patients and make the guidelines less easy to access.

The hospitals we visited had different success rate in reaching treatment goals (Figure 11). Factors that have a positive influence on the results could be high level of education, parents highly involved in the treatment, larger proportion of patients on multi-injection therapy, close follow-up and positive attitude towards T1D and the treatment. We found that in hospitals where the organization of treatment and follow up is close to recommended in guidelines, the treatment goals are still difficult to achieve. In countries where lack of resources and organization of health care makes it difficult to follow guidelines the proportion achieving treatment goals is likely to be smaller.

In all the hospitals the regular checkups are every third month, as recommended in guidelines. This is easy to follow in countries where the health care system is well developed; in other countries this is obviously more difficult.

All the hospitals follow a screening program for autoimmune diseases as recommended in guidelines (Table 13). At UUH and Minneapolis the screening for celiac disease is done more frequently than recommended. The reason for this could be that it is easier to do all the screening annually, this way you don't have to remember when to do the celiac screening. On the other hand taking a test could make the patients feel sicker than they are, make them more aware of symptoms/illness. Screening annually from diagnosis would be the easiest guideline recommendation to remember, but it would be more expensive. A screening program for associated autoimmune diseases is well established in clinical research, but if there is lack of resources this would be less important to pursue.

Screening for late complications is also done at all the hospitals as recommended in guidelines (Table 14). This is an important screening program because the complications cause high morbidity

and mortality. The availability of eye doctors is important and is likely to be the major difficulty in some countries. The treatment of established complications is expensive and probably not available in all countries, this makes screening and prevention of progression to clinical disease even more important.

12.4 Quality of life and mental health

Acute complications are present in a low frequency at all the hospitals (Table 15). The optimal would definitely be no episodes, but this is challenging while at the same time aiming for optimal glycemic control. Only in areas where availability of knowledge and treatment equipment is good, this is within the possible range.

We found that long term complications are rare in children younger than 15 years of age (Table 16). This result reflects the advantage of an organized health care system; close follow up and monitoring of T1D has an impact on the outcome of the disease. It is important to work for inexpensive and simple treatment equipment distributed to all people in the world in the future.

Quality of life is an important aspect to consider in chronic diseases. The choice of insulin regimen has a great influence on the everyday life of children with T1D. Flexibility in diet and level of activity is important to feel as other children. In our opinion this was not accomplished at CHOC where the patients were on a strict diet and had to eat after their dose of insulin. For the children it is important to know that they are not alone in having the disease. They should think of themselves as normal children only with T1D in addition. To obtain this it is important to avoid words as diabetics and instead be consequent on the difference between the child and the disease. Other important arenas are meeting places for children with T1D where they can see that children with the disease do not look different than others. Patient organizations for diabetes play an important role in this matter. In USA the ADA and other patient organizations arrange among other things summer camps only for children with diabetes. In Norway this is organized through NDA. During our visit at camp Needlepoint we saw the positive impact this had on the children.

12.5 Concluding remarks

Internationally accepted guidelines are helpful in diagnostics, treatment and follow up of patients with chronic diseases. They help secure consistency. The optimal would be agreement on one set of guidelines only, preferably with alternative strategies in areas with limited resources. However, there will always be challenges regarding the practical organization and implementation in clinical practice. We visited three hospitals where the availability of resources was good, yet there were still difficulties in following all the guideline recommendations. This could be a challenge for implementation of guidelines in the third world.

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